

Synthetic Organic Chemicals

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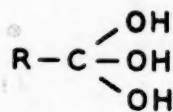
No. 4

Some Reactions and Applications of Orthoesters

GEORGE W. SAWDEY

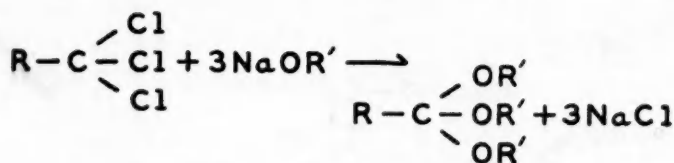
Research Laboratories—Eastman Kodak Company

ESTERS of hypothetical orthoacids, which may be represented by adding the elements of a molecule of water to the normal acid, viz.,



have been known since the early nineteenth century. They possess to an accentuated degree the characteristic spicy odor of ordinary esters and acetals. The lower members of the aliphatic series have some slight hypnotic power; otherwise, they have no appreciable physiological effect.

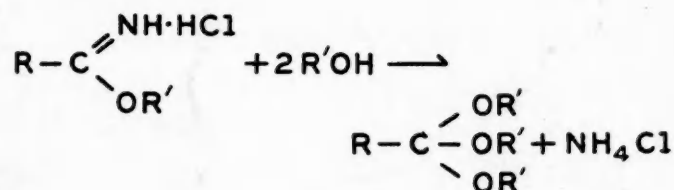
There are two methods in general use for the preparation of orthoesters. The first, historically speaking, is a modification of the Williamson synthesis of ethers. It consists in the reaction of a molecule of chloroform, or substituted chloroform, and three molecules of sodium alcoholate:



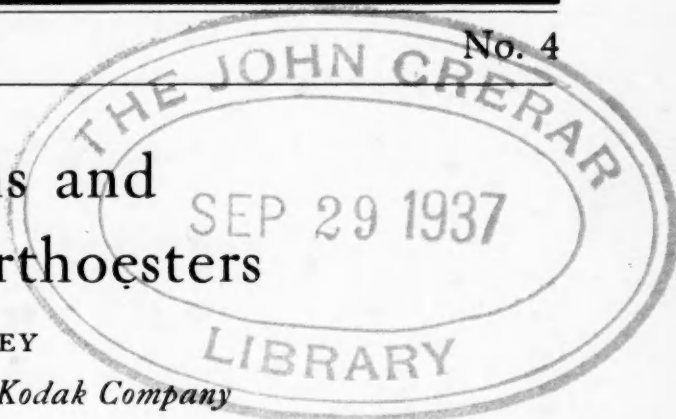
Although it was used by Geuther in 1871 for the synthesis of ethyl ortho-

acetate from methyl chloroform, the method now is chiefly confined to the preparation of orthoformates. The use of higher homologs of chloroform requires that the reaction be carried out under pressure.

The second method, upon which no such limitation is placed, was developed by Pinner (1883) and consists in the alcoholysis of an iminoester hydrochloride:

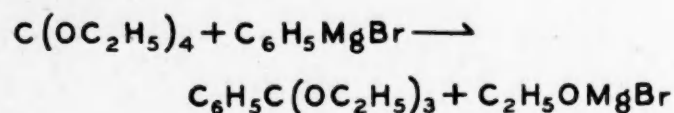


The intermediate used in this synthesis is prepared by passing dry hydrogen chloride gas into an equimolecular mixture of the proper nitrile and alcohol in an inert solvent, such as ethyl ether, iso-propyl ether, or benzene. It is obvious that this method may have a wide application. The iminoester hydrochlorides, aside from their use in the orthoester synthesis, display a wide variety of reactions. Thus, they react with ammonia or primary aliphatic and aromatic amines to form amidines; they react with acetic anhydride to form



iminoacid anhydrides; and they may be used in the Grignard synthesis.

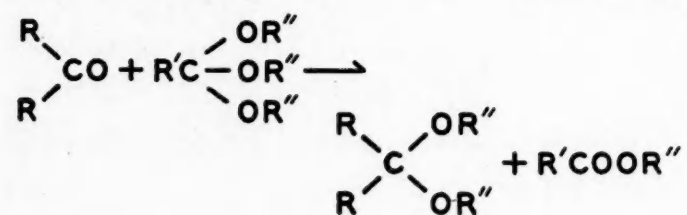
A third method for the synthesis of orthoesters, devised by Tschitschibabine in 1905, involves the treatment of ethyl orthocarbonate with a Grignard reagent, e.g., phenyl magnesium bromide:



Although the orthoesters in the dry neutral state may be assumed to be stable, they decompose easily and rapidly in the presence of water and dilute acids. The constant for the acid hydrolysis of ethyl orthoacetate, in which the normal ester and alcohol are produced, is said to approach the magnitude of 10^6 at 25°C .

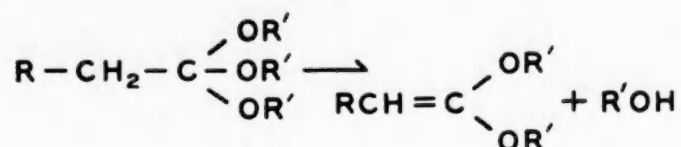
The reactivity of the alkoxy groups illustrated above, possessed presumably in equal degree by all the members, is the basis for the large number of applications which these compounds have found in synthetic organic chemistry. It is proposed to discuss a few of the more general ones in this paper.

It was found by Claisen (about 1895) that aldehydes and ketones reacted with orthoesters, giving acetals and ketals:

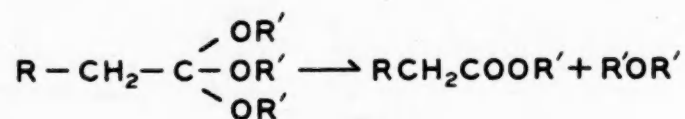


The mechanism of the reaction has not been definitely established. The presence of a catalyst, such as mineral acid, ammonium chloride or ferric chloride, as well as a solvent consisting of methyl alcohol, ethyl alcohol or ethyl ether, seems to be necessary. The rôle of the solvent is not quite clear. Post (1933) found that no reaction occurred when higher alcohols, such as iso-amyl alcohol, were used as solvents.

Sigmund and Herschdoerfer (1931) investigated the reaction of aluminium oxide and orthoesters at elevated temperatures. Interestingly, it was found that the reaction might take either of two courses independently of reaction temperature, but depending on the individual ester. In the one case, a ketene acetal was produced:

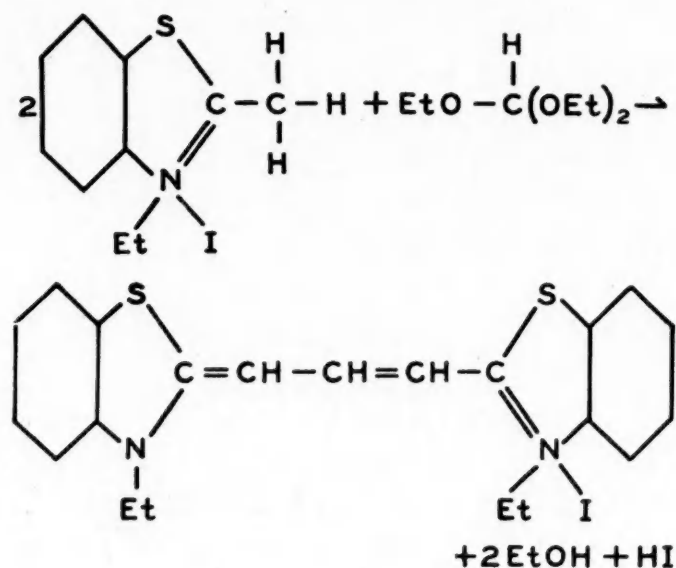


As an alternative, ether might be split out with formation of the normal ester:



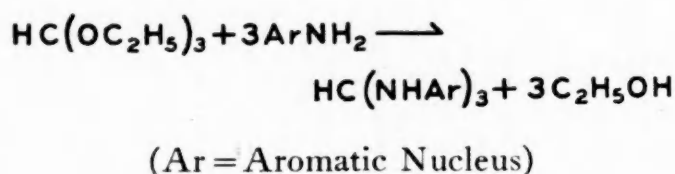
The orthoformate series is excluded from the first type of reaction unless the existence of Scheibler's carbon monoxide acetal be conceded.

König (1922) found that ethyl orthoformate condensed with two molecules of certain heterocyclic quaternary salts containing a reactive methyl group, with the formation of carbocyanine dyes containing the chain $=\text{CH}-\text{CH}=\text{CH}-$, the central CH group being supplied by the orthoester. Where the quaternary salt is 1-methylbenzothiazole ethiodide, the reaction may be written:

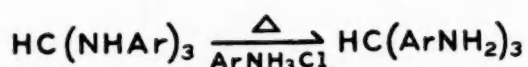


Hamer (1928) described the preparation of thiacyanine dyes containing the chain $=CH-CMe=CH-$ from ethyl orthoacetate. Brooker and White prepared orthoesters of carboxylic acids of higher molecular weight from which they found that certain carbocyanine dyes (patented 1933) containing the chain $=CH-CR=CH-$ (R representing an organic radical of two or more carbon atoms) could be prepared.

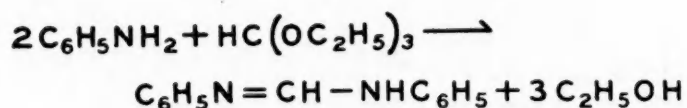
Orthoesters may be used not only in the preparation of cyanine dyes, but in those of the triphenylmethane series as well. Giacalone found (1932) that ethyl orthoformate condensed with primary aromatic amines to give isomers of leuco bases of triphenylmethane dyes:



On heating the anilide with the hydrochloride of the base from which it was formed, a rearrangement took place giving the true leuco base:

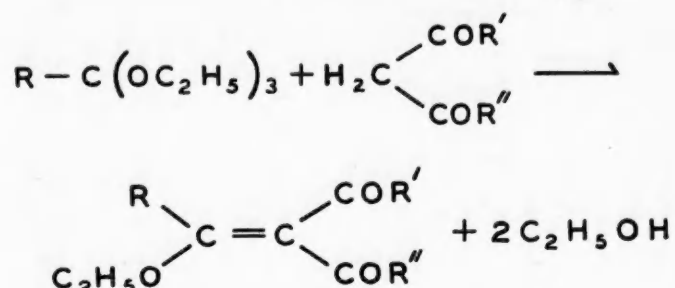


A reaction somewhat similar in nature was carried out by Claisen in 1895. In this, two molecules of aniline condensed with one molecule of ethyl orthoformate to produce diphenylformamidine:

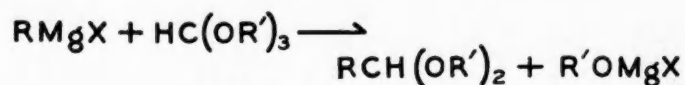


In 1931, Sah studied the condensation of ethyl orthoacetate and methyl orthobenzoate with malonic and acetoacetic esters. The products were methyl and

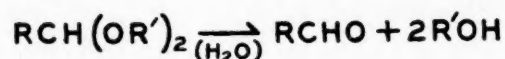
phenyl substituted hydroxymethylene acids. With malonic ester, for example:



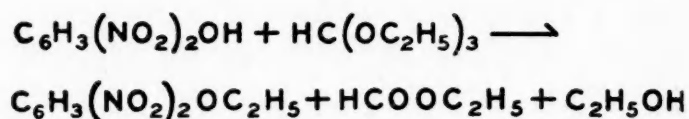
The reaction of ethyl orthoformate with the Grignard reagent was introduced by G. B. Bachman (1933) as a general method for the production of long chain aliphatic aldehydes. In the first reaction an acetal is produced:



which on acid hydrolysis gives the aldehyde:



A reaction which is perhaps of more theoretical than practical interest, namely, the etherification of phenols with orthoesters, was discovered by von Walther in 1915. He was successful in preparing di- and trinitrophenetols by refluxing the corresponding nitrophenols with ethyl orthoformate:



The few reactions described and examples given do not by any means exhaust the possibilities of this interesting series of compounds. Wide individual variations are displayed both in respect to the acid component and the alcohol function, and particular applications naturally follow therefrom. For a complete picture, the reader is referred to the extensive literature on the subject.

Eastman Organic Chemicals as Analytical Reagents

XLIII REAGENTS FOR IRON

RESACETOPHENONE

Cooper, *IND. ENG. CHEM. (ANAL. ED.)*,
9, 334 (1937)

Resacetophenone (2,4-dihydroxyacetophenone) reacts with ferric iron to produce a red color. By this method it is possible to detect ferric iron in concentrations of 2 parts per million. The reagent is prepared by dissolving 10 grams of resacetophenone in 100 c.c. of 95% alcohol. Two drops of the solution are added to 1 c.c. of a slightly acid solution of the unknown in a watch glass, and the appearance of the red color noted, indicating the presence of ferric iron.

Interference of other salts in the detection is not great, as they can be present in large amounts without affecting the reaction.

7-iodo-8-HYDROXYQUINOLINE-5-SULFONIC ACID

Yoe and Hall, *J.A.C.S.*, 59, 872
(1937)

A green color is formed when 7-iodo-8-hydroxyquinoline-5-sulfonic acid is added to a solution containing ferric ions, the intensity varying with the iron concentration. Ferrous iron does not interfere, and the sensitivity is 1 part per million.

The unknown solution is adjusted to approximately pH 2.5 with hydrochloric acid—potassium hydrogen phthalate buffer. To this is added a saturated aqueous solution of the reagent in molecular proportions of at least 3 to 1. The resulting solution is diluted to the mark, and the green color compared with standards of approximately the same iron content.

A Convenient Adapter

The adapter shown in the accompanying diagram was designed to permit either the return of condensed vapor to the boiling flask from which it came or the collection and withdrawal of it externally. The apparatus has been found useful for a number of purposes in the research laboratory, particularly for operations where refluxing is followed by distillation or the reverse, as, for example, in certain Grignard reactions in which one solvent must be replaced by another that has a higher boiling point. The purification of some solvents is carried out by drying the solvent at its boiling point and then distilling, and, in such cases, the adapter is exceedingly helpful. Very often in steam distillations, samples must be collected at frequent intervals to determine the end of the distillation. The ease of withdrawing such samples with this apparatus is evident.

If a second condenser is attached to the outlet tube of the adapter, very rapid distillation even of water can be accomplished. These are only a few of the many applications to which the equipment is suited.

